Systematic review: Mortality and clinical cure rates for pneumonia: a systematic review, meta-analysis, and trial sequential analysis of randomized control trials comparing bactericidal and bacteriostatic antibiotic treatments

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Abstract

Background: Bactericidal antibiotics are generally assumed to be superior to bacteriostatic antibiotics as first-line treatment for pneumonia.

Objectives: We performed a systematic review, meta-analysis, and trial sequential analysis (TSA) of randomized controlled trials (RCTs) of bactericidal versus bacteriostatic antibiotics to ascertain clinical superiority. Clinical cure rate was the primary outcome. Secondary outcomes included all-cause mortality, microbiological eradication, treatment failure, and relapse rates.

Data sources: PubMed, Cochrane Library, Embase, and MedRxiv

Study eligibility criteria: Randomized control trials.

Participants: Adult patients with bacterial pneumonia treated with antibiotics in the community or in-hospital.

Interventions: Bacteriostatic versus bactericidal antibiotics.

Assessment of risk of bias: The Cochrane Collaboration assessing risk of bias 2 tool.

Methods of data synthesis: Data on dichotomous outcomes are presented as risk ratio (RR). A random-effects model with the generic Mantel-Haenszel method was used for integrating RRs for generalizability of findings. The I2 method was used to assess the magnitude of variation secondary to heterogeneity.

Results: Forty-three RCTs involving 10 752 patients met the eligibility criteria. The clinical cure rate (42 studies, 10 312 patients; RR: 1.02; 95% CI, 0.99e1.05; I2: 37%; TSA-adjusted CI, 0.99e1.05), all-cause mortality (25 studies, 8302 patients; RR: 1.07; 95% CI, 0.81e1.42; I2: 57%), microbiological eradication (24 studies, 2776 patients; RR: 1.00; 95% CI, 0.97e1.03; I2: 0%), treatment failure (31 studies, 7296 patients; RR: 0.96; 95% CI, 0.83e1.11; I2: 42%), and relapse rate (5 studies, 1111 patients; RR: 1.15; 95% CI, 0.50e2.63; I2: 0%) were similar between bactericidal and bacteriostatic antibiotic treatments. Conclusions: Bactericidal agents are not associated with any statistical difference in clinical cure rates, mortality, microbiological eradication, treatment failure, or relapse rates compared with bacteriostatic antibiotics in the treatment of pneumonia

Introduction

Bacterial pneumonia remains associated with significant mortality and morbidity [1]. Mortality rates of 30% to 50% are reported for patients with community-acquired pneumonia requiring hospitalization [2] and 20% to 60% for patients who develop hospital-acquired pneumonia [3]. There is an ongoing debate regarding whether bactericidal antimicrobials can be considered superior to bacteriostatic antimicrobials, with an erroneous and traditional belief that the former directly kill pathogens whereas bacteriostatic antimicrobial therapy halts the growth of the microorganisms [4,5].
The formal definition of a bactericidal antibiotic is a ratio of minimum bactericidal concentration to minimum inhibitory con-centration of <4, whereas a bacteriostatic agent has a minimum bactericidal concentration to minimum inhibitory concentration ratio of >4[4]. This definition, however, is arbitrary, with certain bacteriostatic antibiotics being able to kill pathogens at higher concentrations [4]. In fact, some antibiotics, such as linezolid and vancomycin, clearly demonstrate bacteriostatic activity against some bacteria, but also bactericidal activity against others at different concentrations [6,7].

A systematic review that included 13 randomized clinical trials (RCTs) of patients with pneumonia did not find superiority of bactericidal over bacteriostatic antibiotics in terms of clinical cure or mortality rates but did not report other important outcomes [4,8]. Thus, we performed an up-to-date meta-analysis to evaluate, not only clinical efficacy (clinical cure and mortality) but also microbiological eradication, treatment failure and relapse rates. In addition, we performed a trial sequential analysis (TSA) to ascertain the requirement for further clinical trials.

Methods

PROSPERO registration

This review was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42021257094) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Appendix S1 supplemental information).

Information source and search strategy

We conducted a systematic electronic search of PubMed, Cochrane Library, Embase, and MedRxiv using a controlled vocabulary (MeSH) and keywords. We also reviewed relevant references of the included studies and conference proceedings. Date and language restrictions were not applied. The last search update was performed on the 12 October 2021. The Boolean search strategy was performed as follows: ((Pneumonia OR Lower respiratory tract infection OR chest infection)) AND (Antibiotic OR anti-bacterial agent OR bacteriostatic OR bactericidal agent) AND (Clinical trial OR Randomized trial OR Randomised trial OR RCT)). Control group and outcomes were not defined in the search terms to maximize the scope of relevant articles. Research papers and review articles were hand-searched for further relevant trials.

Study selection

Two investigators (NS, FR) independently screened titles and abstracts. Discrepancies regarding the selection of studies for the current review were resolved by a third author (TS). Relevant full-text articles were retrieved and analyzed for selection using the predefined inclusion criteria.

Primary and secondary outcomes

Clinical cure rate was selected as the primary outcome in this meta-analysis. This was defined as the resolution of clinical signs and symptoms at the end of treatment or the end of follow-up, without new onset of symptoms, any complication, or need for further antimicrobial therapy.

Secondary outcomes included all-cause mortality, treatment failure, and relapse rates. Treatment failure was defined as lack of improvement in clinical signs and symptoms during or after treatment. Relapse was defined as initial improvement or resolution of clinical signs and symptoms with recurrence of clinical or radiological manifestations at the time of follow-up. Microbiological eradication was defined as presumed or documented eradication of all pathogens present at baseline.

Data extraction and analysis

Two investigators (NS, FR) independently extracted information from the selected studies using a standardized data collection form. Data were collected on the country of trial, recruitment period, total number of participants, and age and number of patients with pneumonia receiving either bacteriostatic or bactericidal antibiotics at the time of enrolment. Where intention-to-treat and per-protocol analyses were both reported, we used the intention-to-treat data for analysis.

Subgroup analysis

A subgroup analysis was performed separating patients with community-acquired and hospital-acquired pneumonia. An additional subgroup analysis was performed to demonstrate whether specific antibiotics (i.e. oxazolidinones vs. glycopeptides, macrolides vs. fluoroquinolones and macrolides vs. penicillin) showed superiority for the management of community- or hospital-acquired pneumonia.

Risk of bias assessment

The Cochrane Collaboration tool for assessing the risk of bias (RoB2) was used to assess the methodological quality of the RCTs [9]. All included studies were of low quality and at high risk of bias. Therefore, the overall risk of bias at the trial level, rather than outcome level, was assessed. This assessment was performed independently by two authors (NS, FR), with any discrepancies regarding study selection reconciled by a third author (TS). This included the following domains for assessment of trials: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome, incomplete outcome data, selective reporting, and other biases. The risk of bias in each domain was classified as low, high, or unclear.

Grading quality of evidence

The quality of evidence for each outcome measure was assessed per the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (GRADEpro Guideline Development Tool McMaster University, 2015) [10]. Quality was down-graded based on the following certainty assessments: risk of bias, inconsistency,

indirectness, imprecision, and other considerations. The overall quality of evidence was subsequently rated as very low, low, moderate, or high.

Data synthesis and analysis

Data synthesis was performed using Review Manager (version 5.4, Cochrane Collaboration, Oxford, UK). The I2 method was used to assess the magnitude of variation secondary to heterogeneity. All p-values were two-tailed and considered statistically significant at <0.05. Data on dichotomous outcomes are presented as risk ratio (RR), and 95% CIs are given for greater generalizability of the study findings.

A random-effects model with the generic Mantel-Haenszel method was preferred for integrating RRs for greater generalizability of findings. Heterogeneity among original studies and sub-groups was evaluated graphically as a forest plot, along with the I2 statistics, where an I2 of 0% indicates no heterogeneity, 0% < I2 < 30% indicates the least heterogeneity, 30% < I2 < 50% indicates moderate heterogeneity, 50% < I2 < 75% indicates substantial heterogeneity, and values > 75% indicate considerable heterogeneity. Publication bias was assessed using a funnel plot.

A TSA was performed using the TSA program, version 0$9$5$10 (www.ctu.dk/tsa) because type I errors may occur in meta-analyses with sample sizes that are too small. A TSA tests the credibility of the meta-analysis results by combining an estimation of the required information size calculated from the cumulative sample size of the included trials, with an adjusted threshold for statistical significance. Meta-analysis monitoring boundaries (trial sequential monitoring boundaries) and the required information size were quantified, alongside diversity-adjusted information size (D2) and adjusted 95% CIs. Diversity adjustment was performed according to an overall type I error of 5% and power of 80%. To demonstrate the clinical efficacy and safety of bacteriostatic and bactericidal anti-microbial chemotherapy for the treatment of pneumonia, the required information size was calculated using a relative risk reduction of 2.3% based on results of a meta-analysis of RCTs comparing linezolid versus glycopeptide antibiotics for the treatment of suspected methicillin-resistant Staphylococcus aureus nosocomial pneumonia [11].

Publication bias was investigated using a funnel plot in which the standard error of the effect estimate of each study was plotted against the estimate. An asymmetric plot is suggestive of publication bias.

Protocol changes

The final protocol differed from the published PROSPERO protocol in the following ways. The title was changed, with a focus on clinical cure rate and mortality outcomes to increase the study population size. In addition to predefined primary and secondary outcomes, most clinical trials measured mortality at different pre-specified times. Therefore, all-cause mortality was reported as one of the secondary outcomes to maximize the number of patients and to establish a better comparison regarding survival benefits be-tween bactericidal and bacteriostatic antibiotics for the management of pneumonia. An additional sensitivity analysis was performed using the fixed-effect model for clinical cure rate rather than the random-effect model.

Results

Search strategy

The search strategy identified 19 735 results. After removal of duplicates, 18 135 articles remained. Of these, 18 072 were excluded based on title/abstract. Of the remaining 65 studies, 17 were excluded after full-text review because they included comparisons between different bactericidal or bacteriostatic antimicrobial agents [12e28]. A further four studies were excluded due to over-lapping data from other trials [29e32]. One study included the use of co-trimoxazole [33], which has bacteriostatic components but, in combination, may be considered bactericidal. Thus, we excluded this study. Forty-three trials were included in the final analysis, as shown in the Preferred Reporting Items for Systematic Reviews and Meta-analysis flow chart (Table S1, Fig. 1)[34e76].

Risk of bias and GRADE recommendation

Fifteen of 43 trials were open-label studies, resulting in a significant risk of performance bias [34,36,38,42,45,46,51,53,56,60,64, 66,69,71,76]. Thirty-two trials (74.4%) were sponsored by a pharmaceutical company (Table S2)[34,36e39,41,43e49,52e57,59e63,67 ,68,71e76].

Inconsistency in reporting of different secondary out-comes was deemed serious due to substantial heterogeneity in reporting (i.e. >50%). Indirectness was deemed nonserious. Imprecision was judged as nonserious in all domains, excluding clinical cure rate and microbiological clearance, where it was judged to be very serious. Asymmetry in the funnel plot was suggestive of heterogeneity among the published trials (Fig. S1). The overall quality of the evidence using the GRADE assessment was very low (Table 1).

Trial characteristics

Among the 43 trials, 10 752 patients were enrolled with 5175 (48.1%) allocated to bacteriostatic therapy [34e62]. b-lactam anti-biotics, cephalosporins, glycopeptides, fluoroquinolones, and imipenem/colistin were commonly prescribed bactericidal agents (Table S3). Bacteriostatic antimicrobial therapeutics included tigecycline, oxazolidinones, macrolides, sulphonamides, and tetracyclines (Table S3). Twenty-three trials included patients with community-acquired pneumonia who were admitted to the hospital [34,36e38,40e42,44,45,47,49,51,52,56,59e61,65,66,71e73,75], whereas 10 trials included patients with nosocomial pneumonia [43,46,48,50,53,54,56,57,59,62]. The remaining 10 studies reported in- and outpatients with acute bacterial pneumonia as lower respiratory infections [35,63,64,67e70,73,74,76].

Clinical cure rate

Forty-two trials met the inclusion and exclusion criteria, with a total of 10 312 patients [33e69,71e76]. Of these patients, 5175 (50.1%) were treated with bacteriostatic agents and 5137 (49.8%) with bactericidal antibiotics. The mean weighted clinical cure rate reported in all trials was 77.5%. Clinical cure rates were similar between bactericidal and bacteriostatic antimicrobial agents (42 studies, 10 312 patients; RR: 1.02; 95% Cl, 0.99e1.05; I2: 37%; TSA-adjusted Cl, 0.99e1.05; Fig. 2A).

The cumulative Z-curve crossed neither the conventional nor the TSA boundary for benefit or harm. The required information size was not achieved, with only 28.6% of cases accrued, and the boundary for futility was not reached (Fig. 2B).

All-cause mortality

Twenty-five studies reported all-cause mortality, including 8302 patients, of whom 4289 (51.6%) were prescribed bactericidal therapy [34,35,37,38,40,42,43,45,48,52,54e57, 59e63,67,71e75]. The weigh-ted mean mortality was 7.8%, with no difference between patients treated with bactericidal and bacteriostatic antimicrobial agents (25 studies, 8302 patients; RR: 1.07; 95% CI, 0.81e1.42); I2:57%;Fig. 3).

Microbiological eradication

Twenty-four studies reported data on microbiological eradication [36,38,40e45,47e49, 51e54,56,59e61,65,67,72,73,75], including 2776 patients with a combined microbiological eradication rate of 83.2%. Bactericidal chemotherapy was given to 1327 patients (47.8%). No difference in microbiological eradication rate was seen between patients receiving bactericidal and bacteriostatic antimicrobial agents (24 studies, 2776 patients; RR: 1.00; 95% Cl, 0.97e1.03; I2: 0%; Fig. 4).

Treatment failure

Thirty-one studies, including 7296 patients, reported the incidence of treatment failure [34e43,47e52,54,57,58,60e69,72,76]. No difference was observed between patients receiving bactericidal and bacteriostatic agents (31 studies, 7296 patients; RR: 0.96; 95%Cl, 0.83e1.11; I2: 42%; Fig. S2).

Relapse

Relapse rates were reported in five studies [41,52,58,60,67] with no difference in patients receiving bactericidal and bacteriostatic agents (1111 patients; RR: 1.15; 95% Cl, 0.50e2.63; I2: 0%; Fig. S3).

Subgroup analyses

Twenty-three studies included 6549 patients with community-acquired pneumonia. The clinical cure rate was similar between bactericidal and bacteriostatic antibiotics (RR: 1.01; 95% CI, 0.98e1.04; I2: 43%; Fig. S4A). Ten studies, including 2369 patients, found a similar clinical cure rate in patients with hospital-acquired pneumonia (RR: 1.02; 95% CI, 0.93e1.12; I2: 52%; Fig. S4B).

Seven trials including 1274 patients compared oxazolidinones and glycopeptides [43,46,48,53,56,59,74], nine trials including 2926 patients compared macrolides to fluoroquinolones [37,40,41,44,47, 49,52,72,75], and eight trials including 1063 patients compared macrolides with penicillamines [34,36,38,60,63,66,69,73]. No difference in cure rates was seen between oxazolidinones and glycopeptides (RR: 1.02; 95% CI, 0.91e1.185; I2: 51%), macrolides and fluoroquinolones (RR: 0.99; 95% CI, 0.95e1.03; I2: 34%), or macrolides and penicillin (RR: 1.05; 95% CI, 0.97e1.14; I2: 44%), respectively (Fig. S5AeC).

Sensitivity analyses

A fixed-effects model revealed that the cure rate increased with bactericidal compared with bacteriostatic agents (RR: 1.03; 95% CI, 1.00e1.05; I2: 37%; TSA-adjusted CI, 1.0008e1.05; Fig. S6A). The cumulative Z-curve for the fixed-effect model for clinical cure rate crossed both the conventional and TSA boundary, indicating that bactericidal agents were superior (Fig. S6B).

Discussion

In this updated meta-analysis comprising data from 43 randomized trials, there was no statistically significant difference be-tween bactericidal and bacteriostatic antibiotics with regard to clinical cure rate, mortality, and microbiological eradication in the management of pneumonia. This was consistent for both community-acquired and nosocomial pneumonia. Bactericidal antimicrobials offer the theoretical benefit of rapid elimination of microorganisms, limiting the risk of developing resistance or reinfection [5]. It thus appears intuitive that bactericidal antibiotics should offer greater clinical efficacy [4]. However, the lack of clinical benefit seen in this meta-analysis may reflect an oversimplification of bactericidal and bacteriostatic as defined by the mechanism of action. Other factors also affect clinical outcomes in pneumonia and other infections, including host factors such as underlying physiological reserve, comorbidities, and immuno-competence; drug factors, including pharmacokinetics, pharmacodynamics, and tissue penetration; and organism factors such as virulence. This combination of variables could explain the perceived superiority of bactericidal agents in early studies of pneumonia and some other clinical

conditions (i.e. endocarditis, meningitis, and neutropenia), but such distinction is of little relevance when using the clinical outcome as the ultimate guide [8,77].

The theoretical benefit of bactericidal antibiotics producing rapid bacterial eradication may also be offset by an exaggerated host inflammatory response to enhanced release of pathogen-associated molecular patterns after bacterial lysis. This rapid lytic action may thus potentiate adverse clinical outcomes [78]. In a rat caecal ligation and puncture model, bactericidal agents produced an initial hyperinflammatory response compared with one antibiotic-treated animals; although this resulted in increased severity of acute kidney injury, there was faster resolution of inflammation and improved survival [79]. In our meta-analysis, the overall incidence of treatment failure and the total number of adverse events were not statistically different between study groups. However, pathogenic mechanisms that underlie adverse events are again likely to be multifactorial, including residual infection, drug-specific effects, and an enhanced inflammatory response from pathogen-associated molecular patterns released by bacterial death.

In the current meta-analysis, we identified 43 randomized, controlled antibiotic treatment studies in patients with pneumonia, in contrast with the earlier meta-analysis of 13 studies published up to 2012 [5]. However, data must be interpreted cautiously considering the limitations. The microbiological definition of bactericidal and bacteriostatic indicates a degree of separation but is not strongly supported by either preclinical or clinical evidence. Certain bacteriostatic drugs do have bactericidal effects in vitro [80]. It is therefore difficult to predict the action of the drug in terms of bacteriostatic or bactericidal effects in any individual.

The U.S. Food and Drug Administration guidelines (June 2020) state that “the primary efficacy endpoint of clinical success should be defined as an improvement at day 4” [81]. All but one of the studies reported in this analysis predate this guideline and as such have not reported their primary efficacy endpoint under the U.S. Food and Drug Administration guidelines, with significant heterogeneity in the time of follow-up and outcome reporting. The beneficial effect of an antimicrobial is likely dependent on the pathogen load, accessibility to the infecting organism (reduced within an abscess or heavily consolidated

lung tissue), and inter-action with the immune system at the site of infection. Most trials were conducted more than a decade ago, which may affect both internal and external validity as well as generalizability. Most included trials do not report disease severity or length of hospital stay. Furthermore, the pathogenic bacteria itself may affect outcome [82], although none of the trials reported outcome by type of bacteria or the effect of antibiotic choice in the context of resistant bacteria. Not all bactericidal or bacteriostatic antibiotics are equivalent; thus, we attempted to analyse outcomes by specific antibiotic classes but found no differences in clinical cure rates between oxazolidinones and glycopeptides, macrolides and fluoroquinolones, or macrolides with penicillin.

In summary, the current meta-analysis demonstrates that bactericidal agents are not associated with any statistical difference in clinical cure rates, mortality, microbiological eradication, treatment failure, or relapse rates compared with bacteriostatic antibiotics in the treatment of pneumonia. We recommend that the decision regarding empirical therapy be dependent on the clinical condition, antibiotic resistance patterns, and preferred modes of delivery rather than perceived differences in efficacy. Differences in efficacy between antibiotics should be considered, but this should be per antibiotic rather than per their classification to bactericidal or bacteriostatic antibiotics.

Transparency declaration
No funding or conflicts of interest to report. This systematic review and meta-analysis was conducted as a part of a literature search related to a PhD project.

Author contributions
Study conception: NA; literature search: NS and FR; data extraction: NS and FR; assessment of bias: NS and FR; statistics: NS, TS; drafting manuscript: NS, TS; critical review: MS, NA, GS; finalizing manuscript: all authors.

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